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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,697	SIFFERT, WINFRIED	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-19 and 21-37* is/are pending in the application.

4a) Of the above claim(s) *29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-19,21-28 and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election without traverse of group I, claims 13-19, 21-28 and 32-37 in Paper No. 10 is acknowledged.

2. Claims 13-19, 21-28, 32-35 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying human subjects having an increased likelihood of having hypertension wherein the methods comprise detecting the presence of a C to T polymorphism at position 825 of the gene encoding the human G protein β_3 subunit, does not reasonably provide enablement for methods wherein any other alleles of the human G protein β_3 subunit gene are identified as indicative of susceptibility to hypertension or to any other disease or to methods in which the subject is a non-human animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to methods for diagnosing a disease comprising determining the presence of a genetic modification in a gene obtained from a subject which encodes a human G protein β_3 subunit (GNB3). The claims are further limited to methods in which the disorder is one associated with G protein dysregulation. The specification teaches only a single polymorphism in the gene encoding the human G protein β_3 subunit, i.e. the polymorphism of a C to T at position 825 of the human G protein β_3 subunit of SEQ ID NO: 1. The specification reviews the results of a study in which the occurrence of the C825T polymorphism was compared in normal and hypertensive human subjects and concludes that the C825T polymorphism is more prevalent in hypertensive subjects as compared to controls. The

specification is not enabling for the invention as it is broadly claimed for the following reasons: Firstly, the claims include methods in which any modification in the GNB3 gene is detected as indicative of disease. Such modifications include additions, substitutions, deletions and splice variants within the coding and non-coding sequences of GNB3. Yet, the specification has taught only one base pair substitution in the GNB3 gene that is associated with hypertension. The specification does not identify any additional polymorphisms in the human GNB3 gene. Accordingly, the specification has not disclosed a representative number of modifications that fall within the broadly claimed genus of any modification in the GNB3 gene. Additionally, sufficient guidance has not been provided as to how to predictably identify additional members of the broadly claimed genus. There are no teachings in the specification as to other specific regions of the GNB3 gene that would be expected to contain a modification that is associated with the occurrence of disease. To identify additional modifications in the GNB3 gene associated with disease would require extensive experimentation because this would require sequencing the GNB3 gene of individuals having diseases and comparing these sequences with control normal GNB3 sequences, determining which modifications constitute polymorphisms not associated with disease and then trying to identify particular modifications which are statistically relevant and useful for diagnosing a specific disease. Such experimentation is considered to be undue. Accordingly, the ability to establish a correlation between the presence of a polymorphism and the occurrence of a specific disease is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. Further, claims 32-35 appear to encompass

methods of determining an association between a genetic modification and a disorder. These claims as written require searching for novel mutations in the human G protein β_3 subunit gene and then determining which mutations are associated with a disease. Searching for new polymorphisms is considered to essentially constitute a research project. While it is obvious to analyze a gene for the presence of polymorphisms and mutations and while it is within the skill of the art to identify sequence variations, the ability to identify specific mutations and polymorphisms in a gene which are correlated with a specific disease is unpredictable and is only achieved through extensive trial and error experimentation. Secondly, the claims as broadly written include methods for diagnosing any disease or any disorder associated with G protein dysregulation. However, the specification has identified only one disorder, i.e. hypertension, associated with the polymorphism of a C to T at position 825 of the GNB3 gene. No results are presented regarding an association between this polymorphism and the occurrence of any other disease. The post-filing date art corroborates the unpredictability in the art of establishing a correlation between the C825T polymorphisms and increased susceptibility to diseases, including diseases associated with G protein dysfunction. For example, Fogarty (Diabetologia (1998) 31:1304-1308) states that "we have found no evidence for a role of the GNB3 C825T functional variant in the genetic susceptibility to diabetic nephropathy in Type I diabetes, as assessed in a large case-control and family based association study. In addition, there appears to be no significant effect of this polymorphism on variation in blood pressure in this Type I diabetic group" (page 1308). Town (American Journal of Medical Genetics (1998) 88:465-468) reported

that the C825T polymorphism is not associated with risk for Alzheimer's Disease. Haase (Neuroscience Letters 2002. 330: 293-295) teaches that the GNB3 C825T polymorphism is not associated with MS. Kunugi et al (Journal of Neural Transmission (2002) 109: 213-218) teaches that the C825T polymorphism is not associated with schizophrenia or mood disorders. Benjafield (International Journal of Obesity (2001) 25: 777-780) teaches that the C825T polymorphism of GNB3 is not associated with overweight or obesity. Gao teaches that the GNB3 gene appears to be involved in canine cone disease. The reference teaches screening human patients with inherited retinal disease for the presence of mutations in the GNB3 gene. Four mutations were identified in the GNB3 gene, including the C825T mutation. However, Gao teaches that no mutations in the GNB3 gene were found to be associated with the occurrence of inherited retinal degeneration. Thirdly, the specification teaches only the presence of a single C825T polymorphism in the human GNB3 gene. No mutations have been identified in GNB3 genes of other organisms and no association has been established between GNB3 mutations and the occurrence of disease in non-human animals. Again, extensive experimentation would be required to analyze the GNB3 gene sequences of other organisms and identify mutations associated with disease. The specification does not provide specific guidance as to any mutations in the GNB3 genes of non-human animals that would be expected to be associated with any particular disorders. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the

amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate what additional polymorphisms may exist in the G protein β_3 subunit gene and which polymorphisms would be associated with hypertension or any other disease. Furthermore, one cannot readily anticipate whether genetic modifications in the G protein β_3 subunit gene of non-human animals also exist and are correlated with disease. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

3. Claims 13, 14, 15, 18, 19, 32, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods for diagnosing a disease comprising determining the presence of a genetic modification in a gene obtained from a subject which

encodes a human G protein β_3 subunit (GNB3). The specification teaches only a single genetic modification in the GNB3 gene, namely the polymorphism of a C to T at position 825 of the human G protein β_3 subunit of SEQ ID NO: 1. The specification also teaches that this polymorphism is associated with the occurrence of hypertension. While methods which detect the C825T polymorphism of the GNB3 gene the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus of any genetic modification in the GNB3 gene associated with any disease or with disorders associated with G protein dysregulation. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' requires a precise definition, such as by structure, formula, chemical name, or physical

properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only 1 member of the broadly claimed genus of genetic modifications in the GNB3 gene has been identified by its complete structure, i.e. the C to T polymorphism at position 825. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., in terms of functional activity, or in terms of being in linkage disequilibrium with other well characterized polymorphisms, etc). In the instant case, no such identifying characteristics have been provided for any additional polymorphisms. The broadest reasonable interpretation of the claims indicates that the claims are inclusive of a very large genus of polymorphisms present at any position in the GNB3 gene, including the promoter, 3' and 5' untranslated regions, exon and intron regions of the GNB3 gene. While one could contemplate a nucleotide substitution at each and every position in the GNB3 gene, such substitutions are not considered to be equivalent to polymorphisms associated with a disease, particularly diseases correlated with G protein dysfunction. Rather, modifications in the GNB3 gene associated with diseases are represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type GNB3 gene does not allow the skilled artisan to envision all of the contemplated genetic modifications encompassed by the claimed genus. Therefore, Applicants

have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

4. Claims 13-19, 21-28, 32-35 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-19 are indefinite because the claims recite that the method is one for diagnosing a disease, yet the final process step is one for detecting the presence of a genetic modification. The claims do not set forth the relationship between detecting the genetic modification and diagnosing a disease. Therefore, it is unclear as to whether the claims are intended to be limited to method for diagnosing a disease or methods for detecting a genetic modification in the GNB3 gene. Similarly, claims 32-35 are drawn to methods for diagnosing a disorder, yet recite the final step of associating a genetic modification with a disorder. Again, the claims do not recite the relationship between diagnosing a disorder and determining and association between a genetic modification with a disorder.

Claims 21 and 22 are indefinite and confusing because it is unclear as to how this claim is intended to be further limiting from claim 37. Claim 21 recites a method with the additional

limitation that the method includes a step of comparing the gene obtained from a subject with the gene sequence of SEQ ID NO: 1. Yet claim 37, from which claim 21 depends, already includes a step of comparing a subject's GNB3 gene sequence to the gene sequence of SEQ ID NO: 1.

Claim 22 is indefinite over the recitation of "the genetic modification" because this phrase lacks proper antecedent basis. Additionally, it is unclear as to how claim 22 is intended to be further limiting from claim 37. Claim 22 recites the limitation that the method determines the presence of a thymine at position 825. However, claim 37, from which claim 22 depends, already includes a step of detecting a thymine at position 825.

Claims 23-28 are indefinite over the recitation of "the presence of a genetic modification" because it is unclear as to what is intended to be encompassed by the genetic modification. Claim 37, from which claims 23, 26 and 27 depend, recites a step of detecting a thymine at position 825 of the GNB3 gene. However, the claim does not refer to the detection of a genetic modification. Therefore, it is unclear as to whether the genetic modification recited in claims 23, 26 and 27 is intended to refer to the presence of a thymine at position 825 or to another unstated genetic modification.

Claims 32-35 are indefinite over the recitation of "determining the presence of a genetic modification in said gene from the nucleotide sequence of SEQ ID NO: 1" because it is unclear as to what is intended to be meant by this phrase. It is unclear as to whether this is intended to refer to a determining the sequence of SEQ ID NO: 1 or if this is intended to refer to a step of

comparing the nucleotide sequence of a subject's DNA to the nucleotide sequence of SEQ ID NO: 1.

5. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 36 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,242,181. This is a double patenting rejection.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13-19, 21-28, 32-35 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,242,181. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '181 are inclusive of methods which diagnose hypertension by detecting the presence of the C825T GNB3 polymorphism.

7. Claim 36 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-7 of U.S. Patent No. 6,242,181. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '181 are inclusive of methods which diagnose hypertension by detecting the presence of the C825T GNB3 polymorphism.

8. Claims 13-19, 21-28, and 32-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending U.S. Application No. 09/803,653. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '653 are inclusive of methods which diagnose hypertension and diseases associated with G protein dysregulation by detecting the presence of the C825T GNB3 polymorphism.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

December 22, 2002

CARLA J. MYERS
PRIMARY EXAMINER